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EDITOR'S PAGE

When the Trial Is Over

What Secondary Analyses Still Teach Us

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Clinical trials give us answers, but rarely the last word. Once the prespecified endpoints are reported and the paper is published, the data continue to yield insights. Each new analysis offers a different perspective: longer follow-up, refined endpoints, modeling of combined evidence, or deeper looks at biology and structure.

This issue of *JACC* is built around such work. Every major contribution here is a secondary analysis—each revisiting a pivotal trial or data set to ask a new question. Together, they show how science evolves when we look again.

WHEN EVIDENCE AGES: THE DANISH TRIAL, REVISITED

Some secondary analyses extend understanding by adding time. Few illustrate this better than the long-term follow-up of DANISH (DANISH ICD Study in Patients With Dilated Cardiomyopathy).[1]

The original DANISH, published in the *New England Journal of Medicine* in 2016, challenged long-held assumptions about primary-prevention implantable cardioverter-defibrillators in non-ischemic heart failure.[2] The device halved sudden cardiac death but did not lower all-cause mortality—a result that raised a lingering question: Would a survival benefit emerge with longer follow-up?

In this issue, Butt et al[1] provide the most complete answer we are likely to have. After 13 years of follow-up, the benefit on arrhythmic death persists, but no survival advantage emerges. Crossover from the control group to device implantation was modest—about 12% over the entire study period—and sensitivity analyses excluding those patients did not alter the results. The hypothesis that time or treatment drift might reveal a hidden mortality benefit can now be set aside.

We published this analysis because it exemplifies scientific maturity. Long-term follow-up transforms a provocative finding into a stable one. It demonstrates the discipline to test assumptions, revisit evidence, and close lingering questions. The DANISH experience shows that the device's biological effect endures, but its clinical impact does not grow with time—a lesson about both heart failure's evolving biology and the boundaries of preventive device therapy.

> *"Secondary analyses, when guided by good questions, scientific humility, and transparency, are not 'spin.' They are science—exploratory, contingent, and essential."*

EXPLORING NEW ENDPOINTS: THE VICTOR ANALYSIS

A different kind of secondary analysis asks not what happened, but how we measure it. In this issue, Zannad et al[3] revisit the VICTOR (Vericiguat Global Study in Participants With Chronic Heart Failure) trial of vericiguat in stable outpatients with heart failure and reduced ejection fraction. The parent trial's primary endpoint—cardiovascular death or hospitalization for heart failure—was neutral.[4] Yet in contemporary heart failure care, most worsening events no longer require hospitalization. The investigators therefore examined a broader endpoint that includes both outpatient and inpatient decompensations.

The result was exploratory but provocative: a modest signal of benefit when all worsening heart failure events were considered. Importantly, the investigators framed this with restraint. They described the work as hypothesis-generating,

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emphasizing that it is meant to spark discussion, not to change practice.

That is why this contribution deserves attention. It models scientific humility and methodological curiosity—showing how trial data can help us rethink endpoints in a world where patients are more often managed outside the hospital.

WHEN MODELING EXTENDS EVIDENCE—BUT CANNOT REPLACE IT

That exploratory signal gains broader context from Tromp and colleagues,[5,6] who updated their network meta-analysis of disease-modifying therapies for heart failure with reduced ejection fraction to include vericiguat. Their findings reaffirm the established hierarchy: quadruple therapy—angiotensin receptor neprilysin inhibitor, β-blocker, mineralocorticoid receptor agonist, and sodium-glucose cotransporter 2 inhibitor—remains the evidence-based foundation. The investigators go further, estimating that adding vericiguat—a potential "fifth pillar"—could yield an additional 0.7 years of survival, but only if the mortality benefit observed in exploratory analyses is confirmed.

These results are conceptual scaffolding for future trials, not a new basis for practice change. Modeling can project possibilities, not certainties. As editors, our role is to publish such analyses—but also to label them for what they are: thoughtful, hypothesis-generating efforts to extend understanding, not to rewrite the evidence hierarchy.

SURROGATES AND SIGNALS: THE ODYSSEY AND MAPLE ANALYSES

Mechanistic and imaging analyses provide yet another form of secondary insight—revealing how therapies act within the heart, even when the outcomes remain neutral.

In ODYSSEY-HCM (A Study of Mavacamten in Nonobstructive Hypertrophic Cardiomyopathy), Desai et al conducted companion analyses of mavacamten in nonobstructive hypertrophic cardiomyopathy, a condition with no approved therapies. The parent trial, published in the *New England Journal of Medicine*, was clinically neutral at 48 weeks.[7] But the secondary analyses tell a richer story: biomarkers such as N-terminal pro-B-type natriuretic peptide and high-sensitivity troponin I fell by roughly one-half, and detailed echocardiography showed modest reductions in left ventricular wall thickness and improvements in diastolic parameters.[8,9] However, 1 in 5 patients experienced reversible reductions in ejection fraction below 50%, underscoring the importance of ongoing safety monitoring. These findings confirm target engagement while raising important questions: might clinical benefit emerge with longer follow-up, and can these biological changes be achieved safely in broader populations?

By contrast, Hegde et al[10] found clear physiologic and symptomatic benefit of aficamten versus metoprolol in obstructive hypertrophic cardiomyopathy in the MAPLE-HCM (Metoprolol vs Aficamten in Patients With LVOT Obstruction on Exercise Capacity in HCM) trial. Aficamten produced large reductions in left ventricular outflow tract gradients and improved diastolic indices, with less mitral regurgitation and systolic anterior motion, all while preserving systolic function.

Together, these studies highlight the recurring lesson that biological success is not the same as clinical success. Surrogate improvements can illuminate mechanisms and guide next-generation trials, but they cannot substitute for patient-centered outcomes.

WHY WE PUBLISH THESE STUDIES—AND HOW TO READ THEM

Across these examples, the scientific value of secondary analyses is clear. They:

- Extend knowledge—revealing how treatment effects evolve, vary by subgroup, or manifest biologically;
- Refine understanding—showing discordance between surrogate and clinical outcomes and prompting better trial design; and
- Propose hypotheses-offering signals worth testing but not certainties worth acting on.

But secondary analyses also demand editorial discipline. *JACC* publishes them because they teach; we accompany them with context so readers understand what they mean—and what they do not. These studies should inform thought, not dictate action.

The December issue is, in that sense, a masterclass in interpretation. The DANISH long-term follow-up informs shared decision-making about implantable cardioverter-defibrillators in nonischemic cardiomyopathy. The Zannad and Tromp contributions clarify the boundaries of vericiguat's promise. The ODYSSEY and MAPLE analyses show what mechanistic progress looks like in cardiomyopathy drug development. Each contributes to our collective understanding of disease—but none alone changes practice.

The larger message is that cardiovascular medicine advances not only through new trials, but through

disciplined re-examination of old ones. Secondary analyses, when guided by good questions, scientific humility, and transparency, are not "spin." They are science—exploratory, contingent, and essential.

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Dr Krumholz, in the past 3 years, has received options for Element Science and Identifeye and payments from F-Prime for advisory roles; was a co-founder of and held equity in Hugo Health; is a co-founder of and holds equity in Refactor Health and ENSIGHT-AI; is a co-founder of medRxiv; is on the Board of openRxiv (non-paid, volunteer); and is associated with research contracts through Yale University from Janssen, Kenvue, Novartis, and Pfizer.

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